K1.3

K1.3

N20823

N20823

RCP.
5/4/00
9:03 AM

Exelon™

(Rivastigmine Tartrate)

Capsules

[redacted], 1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg

NDA 20-823

Chemistry

CHEMISTRY

NDA 20-823
Exelon™
(Rivastigmine Tartrate) Capsules
1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg
Classification: 1S

Date	Document	Tab
	Labeling & Nomenclature Reviews	C
	7/11/97	
	10/31/97 (2)	
	3/28/00	
	EER: **ACCEPTABLE as of 3/27/2000**	D
9/23/97	ENVIRONMENTAL ASSESSMENT: Minor Amendment from firm Request to Withdraw EA from NDA and claim for Categorical Exclusion	E
12/30/97	Chemistry Review # 1: W. Rzeszotarski, Ph.D.	F
1/7/98	AGENCY LETTER: Minor Deficiency Letter	G
4/2/98	Chemistry Review # 2: W. Rzeszotarski, Ph.D.	H
7/7/98	NOT APPROVABLE Letter to Firm	
Feb, 1999	Chemistry EMails to file	I
2/16/99	Chemistry Review # 3: W. Rzeszotarski, Ph.D.	I
3/4/99	Methods Validation	J
5/12/99	APPROVABLE Letter to Firm	
2/28/00	Chemistry Review # 4: W. Rzeszotarski, Ph.D.	K
3/16/00	Chemistry Review # 5: W. Rzeszotarski, Ph.D.	L
3/27/00	Chemistry Review # 6: W. Rzeszotarski, Ph.D.	M
4/5/00	Email Re: Methods Validation, W. Rzeszotarski, Ph.D.	Mc

Resubmission

Consult # 705

OUTGOING

APR 11 1997

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 10, 1997

FROM: Paul Leber, M.D., Director /S/
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Dan Boring, Chair
Labeling and Nomenclature Committee
HFD-530, Corporate N461

RETURN

APR 1997

Proposed Trademark: **Exelon™ NDA # 20-823**

Established name, including dosage form:

Other trademarks by the same firm for companion products: **None**

Indications for Use (may be a summary if proposed statement is lengthy):

Exelon™ is indicated for the treatment of mild to moderately severe dementia of the Alzheimer's type.

Initial comments from the submitter: (concerns, observations, etc.)

Please note that this proposed Tradename has been previously reviewed by the committee under the IND (Consult # 705). Copy attached.

cc:
ORIG NDA
HFD-120
HFD-120/SBlum/Rzeszotarski
HFD-120/RNighswander 4/11/97

RETURN

JUN 1997

Consult #705 (HFD-120)

EXELON SDZ ENA 713 capsules

The Committee is concerned that the prefix EXEL- suggests excellent and there is some potential for promotional misuse with the proposed name. Additionally, the Committee found one look-alike/sound-alike conflict: ENLON, an injectable skeletal muscle relaxant. However, the Committee feels there is a low potential for confusion.

The USAN name is still pending therefore the comments of the Committee are preliminary pending final adoption of the proposed USAN name. Overall, the Committee finds the name acceptable and requests the name to be resubmitted when the product reaches the NDA stage.

/S/ 17, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 31-Oct-1997 03:42pm EST
From: Dan Boring
BORINGD
Dept: HFD-530 CRP2 N461
Tel No: 301-827-2391 FAX 301-827-2510

TO: Robbin Nighswander (NIGHSWANDER)

Subject: RE: NDA 20-823, Exelon Capsules

Robbin,

The reconsult found no new concerns by the Committee, so it's safe by us. The USAN does not interfere with any other names so it needn't be consulted to us.

thanx,

dan

APPEARS THIS WAY
ON ORIGINAL

IC COMPLETED MAR 2 8 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 2/3/00	DUE DATE: 3/30/00	OPDRA CONSULT #: 00-0052

TO :

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: R. Nighswander, Project Manager, DNDP
HFD-120

PRODUCT NAME: **Exelon®** (rivastigmine), capsules and solution **NDA #:** 21-025, 20-823	**MANUFACTURER:** Novartis Pharmaceuticals Corporation.
Safety Evaluator: Peter Tam, RPh.	

DRA RECOMMENDATION:
DRA has no objections to the use of the proprietary name Exelon®.

/S/ 3/3/2000
Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 3/7/00
Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 3/14/00

NDA#: 20-823
21-025

Name of Drug: Exelon®
(rivastigmine), capsules and solution

NDA Holder: Novartis Pharmaceuticals Corporation.

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) on February 3, 2000, to review the proposed proprietary drug name, Exelon® in regard to potential name confusion with existing proprietary/generic drug names.

a sponsor for Aricept® and copromoter with Pfizer Inc., filed a complaint with the DDMAC on 10/2/1998 about the proposed trade name of Exelon®. elt that the proposed proprietary name Exelon® is false and misleading. A study, sponsored by , had been undertaken by vhich specializes in healthcare marketing. For this study, conducted telephone interviews of 100 randomly selected physicians. They were asked about their awareness of other Alzheimer's therapies, their perceptions of the proprietary name "Exelon®. Survey results demonstrate that proposed name "Exelon" implies a claim of excellence and superiority. claims that the use (if approved) of such a name in product lebeling or advertising would be false and misleading and would misbrand the drug in violation of the Act (21 CFR 201-10(c)(3) and 202.1(a)(3).

The Labeling and Nomenclature Committee (LNC) had reviewed this proprietary name on 1/7/97 when it was filed under IND application. LNC found the name acceptable. However, the committee was concerned that the prefix "EXEL" suggested excellent and there was some potential for promotional misuse with the proposed name. LNC requested the name to be resubmitted when the product reached the NDA stage. When this proposed name, Exelon® was resubmitted for evaluation by LNC on 6/23/97 (NDA stage), LNC found the proposed proprietary

name acceptable. There were still no look-alike and sound-alike names found.

PRODUCT FORMATION

Exelon® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. It is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. It is also rapidly and extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Half-life in plasma is approximately 1.6 hours. The major pathway of elimination is via the kidneys.

Rivastigmine exhibits linear kinetics over the dosing range of 1-3 mg bid. At higher doses of 3-6 mg bid, it tends to display nonlinear kinetics; doubling the dose from 3 to 6 mg bid results in a 3-fold increase in AUC (area under the curve). There is no accumulation of rivastigmine in Alzheimer's patients and steady state is reached within 1 day of dosing.

The recommended starting dose of Exelon® is 1.5 mg twice a day. If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. The maximum dose is 6 mg bid (12 mg/day).

Exelon® will be supplied as 1.5 mg, 3 mg, 4.5 mg and 6 mg of capsule in bottles of 60, 500 and unit dose package of 100. Oral solution will be supplied as 2 mg/ml in bottle of 120 ml.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Exelon® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparisons (update monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline, Decision Support System (DSS), Establishment Evaluation System, and LNC database. An expert panel discussion was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing healthcare practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process.

A. EXPERT PANEL DISCUSSION:

The expert panel consists of members of OPDRA medication error safety evaluator staff and a representative from the Division of Drug Marketing, Advertising and Communication.

The panel discussion was conducted on 2/22/00. There were no problems found with other similar sounding or looking proprietary drug product names. However, DDMAC expressed concerns about the prefix "exel" portion of the name which might indicate greater efficacy and is promotional.

B. STUDY CONDUCTED BY OPDRA

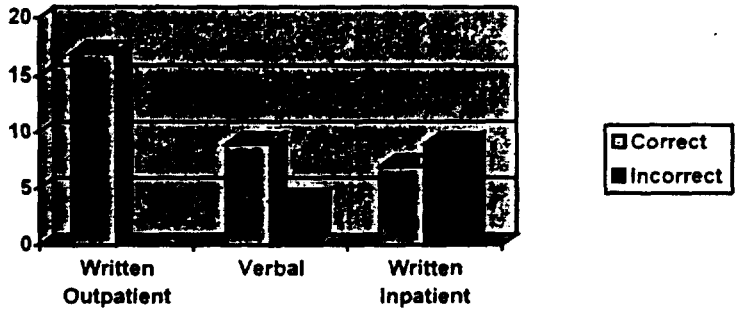
Methodology:

This study involved 92 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Combidex® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An OPDRA staff member wrote three outpatient prescriptions, one consisting of a known drug product, one is for Exelon® and the other one is unknown (unapproved) name. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating healthcare professionals via e-mail. In addition, four inpatient prescriptions were written, one consisting of a known drug, one is for Exelon® and the other two are unknown (unapproved) proprietary names. Written inpatient and outpatient prescriptions were sent to 31 participants each for review. In addition, one medication error staff recorded the inpatient orders on voice mail. The voice mail messages were then sent to 30 participating healthcare professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We recognize that our sample size is small and the study is designed to increase the likelihood of detecting failures.

The results are summarized in Table I.

Table I

Study	# of Samples	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	31	17 (55%)	17	0
Verbal	30	13 (43%)	9	4
Written Inpatient	31	16 (52%)	7	9
Total	92	46 (50%)	33	13



Seventy-two percent of the participants responded with the correct name Exelon®. The incorrect written and verbal responses are as follows in Table II.

Table II

	Incorrectly Interpret
Inpatient Written	Exelcin (5)
	Exelin (2)
	Cxelen
	Excedrin*
Verbal	Phonetic Variable Responses
	Hexalon
	Xylon
	Mexalon
	Xalon

* Currently marketed proprietary name

C. CONTAINER LABEL, CARTON AND INSERT LABELING:

1. Current USP nomenclature standards, under General Notices, recommend that the strength of a drug product is expressed on the container label in terms of milligrams or micrograms or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

   In this case, we believe it is less confusing and allows greater utilization of container label space as shown below:

   Exelon®
   (rivastigmine capsules)
   1.5 mg

   The Description section of the package insert should state:

2.

3.

D. CONCLUSIONS:

Results of the verbal and written analysis studies show 33 participants interpreted proprietary name Exelon® correctly. However, the were 13 inaccurate interpretations in written and verbal pronunciation. There was one interpretation that overlapped with an existing approved drug product, Excedrin, in our written inpatient prescription study. This was not what we predicted in the expert panel discussion, and is a significant finding in a study with a small sample size. However, to put Exelon® in its clinical perspective, several factors have to be considered such as to how and when the drug will be used and what

kind of patient population that will use this drug.

First, Exelon® is a capsule formulation and is available in the following strengths 1.5 mg, 3 mg, 4.5 mg and 6 mg. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. The recommended starting dose of Exelon® is from 1.5 mg to 3 mg bid. Excedrin is an OTC tablet product mostly used for minor pains and is dosed on as needed basis. Second, when the sound-alike and look-alike name such as Excedrin is ordered verbally or in written order in an inpatient setting for the treatment of Alzheimer, it will be highly unlikely that Excedrin misinterpreted for Exelon® will be dispensed without seeking clarification on dosing and strength by the dispensing pharmacists. Furthermore, since there is no overlapping administration dosing schedule and strength between Exelon ® and Excedrin, the potential safety risks for confusion is hence decreased.

Finally, the studies and searches conducted within FDA did not reveal any other existing drug names that would render the proposed proprietary name, Exelon® objectionable.

III. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name Exelon®.

B. DDMAC has no objections to the use of the term "EXEL" for this proprietary name Exelon®.

C. OPDRA recommends the above labeling revisions to encourage the safest possible use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 12000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA 20-823 & 21-025
Office File
HFD-120; R. Nighswander, Project Manager, DNDP
HFD-120; Russell Katz, M.D., Division Director, DNDP
HFD-430; Charlene Flowers, Safety Evaluator, DDRE I
HFD-42; Mark Askine, Senior Regulatory Review Officer, DDMAC
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (electronic copy)
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (electronic copy)

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20823/000
Stamp: 07-APR-1997
Regulatory Due: 21-APR-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1S
Org Code: 120

Action Goal:
District Goal: 06-DEC-1997
Brand Name: EXELON(RIVASTIGMINE TARTRATE)CAPSULES
Estab. Name:
Generic Name: RIVASTIGMINE TARTRATE
[redacted]/1.5MG

Dosage Form: (CAPSULE)
Strength: [redacted] 1.5, 3, 4.5, 6

Application Comment:
FDA Contacts: R. NIGHSWANDER (HFD-120) 301-594-2850 , Project Manager
W. RZESZOTARSKI (HFD-120) 301-594-2850 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation: ACCEPTABLE on 27-MAR-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 21-MAY-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9692043
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CHG OAI Status: NONE
Estab. Comment: NEW ALTERNATE SITE SUBMITTED WITH THE COMPLETE RESPONSE (on 10-JAN-2000 by W. RZESZOTARSKI (HFD-120) 301-594-2850)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-JAN-2000				RZESZOTARS
SUBMITTED TO DO	11-JAN-2000	PS			EGASM
ASSIGNED INSPECTION	21-JAN-2000	PS			EGASM
DO RECOMMENDATION	27-MAR-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
WRONG PROFILE CLASS ASSIGNED ORIGINALLY. FIRM HAS BEEN INSPECTED WITHIN LAST TWO YEARS.					
OC RECOMMENDATION	27-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 2210396
NOVARTIS PHARMA INC (SANDOZ)
59 RT 10
EAST HANOVER, NJ 079361080

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER
Profile: CHG OAI Status: NONE
Estab. Comment: LAST INSPECTION: 8/31/94 (on 11-APR-1997 by PARKS)
RCD ORIG. NJ SITE TO DO RELEASE AND STABILITY TESTING AND PACKAGING, LABEL DTD 4/20/97.FWD MOST TO ITOB EX TM AND SOME STAB INFO. (on 21-APR-1997 by R. BROWN (HFR-CE350) 732-940-8967)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
OC RECOMMENDATION	11-APR-1997			ACCEPTABLE	PARKS

BASED ON PROFILE

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
CH-4002
BASEL, , SZ
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CHG OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
SUBMITTED TO DO	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	14-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-DEC-1997	GMP			IRIVERA
INSPECTION SCHEDULED	03-MAR-1998		27-FEB-1998		EGASM
INSPECTION PERFORMED	21-MAY-1998		23-FEB-1998		EGASM
DO RECOMMENDATION	21-MAY-1998			ACCEPTABLE	EGASM
OC RECOMMENDATION	21-MAY-1998			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Profile: CSN OAI Status: NONE
Estab. Comment: PLEASE NOTE THAT NOVARTIS IS THE RIGHT NAME FOR SANDOZ+CIBA-GEIGY ! (on 10-APR-1997 by BLUMS)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
OC RECOMMENDATION	11-APR-1997			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9614433
NOVARTIS PHARMANALYTICA SA
LOCARNO, , SZ
DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment: NEW ESTABLISHMENT, NOT IN SYSTEM PREVIOUSLY (on 10-APR-1997 by BLUMS)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
SUBMITTED TO DO	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-DEC-1997	GMP			IRIVERA
INSPECTION SCHEDULED	03-MAR-1998		06-MAR-1998		EGASM
INSPECTION PERFORMED	02-APR-1998		05-MAR-1998		EGASM
DO RECOMMENDATION	02-APR-1998			ACCEPTABLE	EGASM
OC RECOMMENDATION	02-APR-1998			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

CONFIDENTIAL

Attachment 1

Marketing forecast for Rivastigmine Base

At the present time, Novartis Pharmaceuticals Corporation [redacted] will be marketed in the US in the year 2001, and [redacted] will be marketed in the year 2002 following approval.

APPEARS THIS WAY
ON ORIGINAL

CONFIDENTIAL

Attachment 2

Calculation of Expected Introduction Concentration (EIC) for Rivastigmine Base entering the aquatic environment from patient use

The Expected Introduction Concentration (EIC) of rivastigmine tartrate (as its corresponding free base) in wastewater effluent due to patient use, assuming all drug substance which has been produced is used, even distribution throughout the US per day, and no metabolism or depletion mechanisms, was calculated as follows:

Expected Introduction Concentration (EIC) for rivastigmine base:

$$EIC = \frac{kg}{yr} \times \frac{1\ day}{\quad} \times \frac{1\ yr}{365\ days} \times \frac{\quad}{kg}$$

$$EIC = \frac{\quad}{yr} \times \frac{1\ day}{\quad} \times \frac{1\ yr}{365\ days} \times \frac{\quad}{kg}$$

EIC = [redacted]

EIC = [redacted]

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

DEC 30 1997

NDA #: 20-823 CHEM.REVIEW # 1 REVIEW DATE: 29-SEP-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	07-APR-97	09-APR-97	10-APR-97

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME
Proprietary: EXELON
Nonproprietary/USAN:
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase

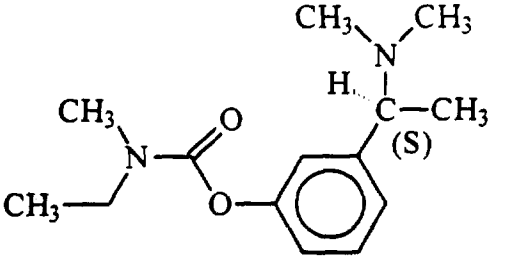
PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type

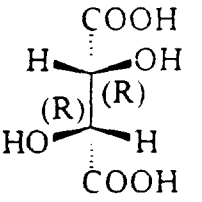
DOSAGE FORM: Capsules
STRENGTHS: , 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS # 129101-54-8





SUPPORTING DOCUMENTS: [redacted]
(see Review Notes)
RELATED DOCUMENTS:
REMARKS/COMMENTS: A stable but hygroscopic compound requiring protection from humidity. Minor deficiencies requiring additional information to resolve them. See Review Notes and the Deficiency Letter.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-823 APPROVABLE subject to resolution of minor issues, acceptable EIR and methods validation.

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

cc
Orig NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-910/JSimmons
RD Init by: MEG 12.20.97

NDA 20-823

JAN 7 1998

Novartis Pharmaceuticals Corporation
Regulatory Affairs
ATTN: Dr Robert W. Kowalski
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr Kowalski:

Reference is made to your New Drug Application (NDA) submitted pursuant tp section 505 (b) of the Federal Food, Drug, and Cosmetic Act for EXELON (carbamoylatine hydrogen tartrate) Capsules.

We have reviewed the Chemistry, Manufacturing and Controls portion of your application and in accord with 21 CFR 314.102 (b) note the following deficiencies:

1. Please identify commercial sources of the intermediate [redacted], and provide a detailed description of the synthesis of intermediates II and III.

2. We notice that some of your regulatory methods for the drug substance are copied from the European Pharmacopeia. Kindly replace them with the USP methods or provide proof of their equivalency.

3. Kindly verify whether the heating rate of [redacted] injector. (see p 3-405 of your CMC part)

4. Please be reminded that the extractable materials in plastic should be determined by the USP <661> and not by the Swiss Alimentary book. Kindly introduce the necessary changes.

5. Please justify your size specifications for cellulose microcrystalline, fine powder and granular powder by providing the results of actual size analysis of batches used in production of drug product.

6. From your list of specifications for the components of drug product and description of tests it is difficult to ascertain which of the tests are to be conducted by the suppliers and which are your acceptance tests. Please identify the acceptance tests for the inactive components of the drug product, empty capsules in particular. We note your remark that: "a certificate of analysis for each empty hard gelatin capsule follows." (5-763) Does it mean that the capsules are accepted on the basis of a certificate of analysis?

7. We realize that the description of the sampling procedures (3-938) is a translation from Schweizerdeutsch. Kindly provide full explanation of the abbreviations used in this text.

8. We note that your specifications for the levels of degradants in the drug product are not supported by the analysis of clinical batches and the reported stability studies. Kindly edit your specifications so they reflect the actual levels observed in the clinical batches and are congruent with the maximal patient exposure.

9. Please provide samples or copies of all container labels.

Should you have any questions please call Mr Robbin Nighswander, Senior Regulatory Project Manager at (301) 594-2850.

Sincerely yours,

/S/

Maryla E. Guzewska, Ph.D.
Acting Chemistry Team Leader, DNDC-1
Division of Neuropharmacological
Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 20-823

cc: Original NDA 20-823
HFD-120/Div. File/
HFD-120/JRzeszotarski/ 8 DEC 97
HFD-120/CSO/RNighswander/
HFD-120/MEGuzewska/ 1.6.98

R/D Init by: MEG

DEFICIENCIES

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS APR 2 1998
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-823 **CHEM.REVIEW #** 2 **REVIEW DATE**: 02-APR-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	27-FEB-98	04-MAR-98	04-MAR-98

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary: EXELON® Capsules
Nonproprietary/USAN: Rivastigmine Tartrate (USAN)
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase

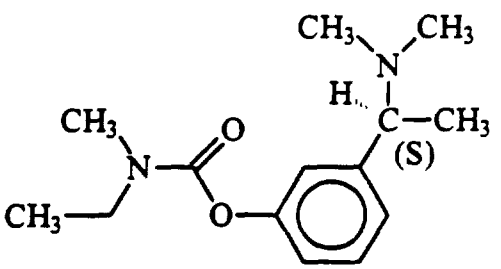
PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type

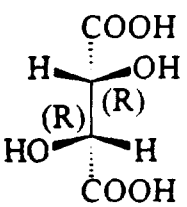
DOSAGE FORM: Capsules
STRENGTHS: [redacted]; 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS # 129101-54-8





SUPPORTING DOCUMENTS: [redacted]
(see Review Notes)
RELATED DOCUMENTS:
REMARKS/COMMENTS: Response to deficiency letter. The samples of copies of container labeling are promised to be send separately and are still to be delivered. The issue of degradant and their levels remains to be resolved. Methods Validation Report has been received. See the attached. See the Review Notes.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-823 APPROVABLE subject to resolution of degradant issue and review of package labels, and acceptable EIR.

cc:
Orig. NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by: MEG 4.29.98

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

CDER Establishment Evaluation Report for April 02, 1998

Application: **NDA 20823/000**
Stamp: **07-APR-1997** Regulatory Due: **07-JUL-1998**
Applicant: **NOVARTIS PHARMS**
59 RT 10
EAST HANOVER, NJ 079361080

Priority: **1S** Org Code: **120**
Action Goal: District Goal: **06-DEC-1997**
Brand Name: **EXELON**
Established Name:
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **1.5, 3, 4.5, 6**

FDA Contacts: **R. NIGHSWANDER (HFD-120)** **301-594-2850 , Project Manager**
W. RZESZOTARSKI (HFD-120) **301-594-2850 , Review Chemist**

Overall Recommendation:

Establishment: **2210396**
NOVARTIS PHARMA INC (SANDOZ)
59 RT 10
EAST HANOVER, NJ 079361080

DMF No:

AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 11-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Establishment: **9611204**
NOVARTIS PHARMA INC (SANDOZ)
LICHTSTRASSE 35
BASEL, , SZ ch-4002

DMF No:

AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **INSPECTION SCHED 03-MAR-1998**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 11-APR-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **9614433**
NOVARTIS PHARMANALYTICA SA
VIA SERAFINO BALESTRA 31
LOCARNO, , SZ

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 02-APR-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE STABILITY TESTER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
Division of Testing and Applied Analytical Development
St. Louis, MO 63101
Tel. (314) 539-2011 Ext. 140
FAX Tel. (314) 539-2113

Date : March 31, 1998

From : B.J.Westenberger, Chemist
FDA/DTAAD/STL, HFD-920

/S/

Subject : NDA 20-823, EXELON Bulk Drug and Capsules

TO : W. Janusz Rzeszotarski, Ph.D., Review Chemist, HFD-120

Through: Moheb M. Nasr, Ph.D., Deputy Director, Lab I, HFD-920

The requested determinations for Exelon both drug substance and final dosage forms have been completed. The methods evaluated are suitable for quality control and regulatory purposes.

One comment deserves mentioning regarding the HPLC procedures that specify mixing the organic with the aqueous and then adjusting the pH. It is generally recognized as a better technique to adjust the pH of the aqueous component first and then to mix with the organic component.

Printed by Robbin Nighswander

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 02-Feb-1999 10:30am
From: Janusz Rzeszotarski
RZESZOTARSKI
Dept: HFD-120 WOC2 4009
Tel No: 301-594-2850 FAX 301-594-2859

TO: Robbin Nighswander (NIGHSWANDER)

CC: Maria Guzewska (GUZEWSKAM)
CC: John Simmons (SIMMONSJ)
Subject: Rivastigmine tartrate as USAN name

Robbin, Greetings:

Please clarify whether Novartis obtained the USAN approval for rivastigmine tartrate. The last document I have is a copy of April 10, 1997 request for consult (from Dan Boring) indicating that the sponsor is awaiting approval. The 1997 USP Dictionary does not list that compound.

Also refer to my E-mail of yesterday re labels.

Janusz

APPEARS THIS WAY
ON ORIGINAL

Printed by Robbin Nighswander

Electronic Mail Message

'ivity: COMPANY CONFIDENTIAL

Date: 10-Feb-1999 10:57am
From: Janusz Rzeszotarski
RZESZOTARSKI
Dept: HFD-120 WOC2 4009
Tel No: 301-594-2850 FAX 301-594-2859

TO: Russell Katz (KATZR)
TO: Maria Guzewska (GUZEWSKAM)
TO: Robbin Nighswander (NIGHSWANDER)

CC: John Simmons (SIMMONSJ)
Subject: Rivastigmine tartrate (USAN)

Amtgenossen, Greetings:

It is official by Bob Clark of Novartis. They do have a letter approving the name. He promised to fax me a copy. He also mentioned that they will edit they labeling document to

latter.

Janusz

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-823 **CHEM.REVIEW #** 3 **REVIEW DATE:** 16-FEB-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL AMENDMENT	27-JAN-99	28-JAN-99	28-JAN-99

NAME & ADDRESS OF APPLICANT:

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary: EXELON® Capsules
Nonproprietary/USAN: Rivastigmine Tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase

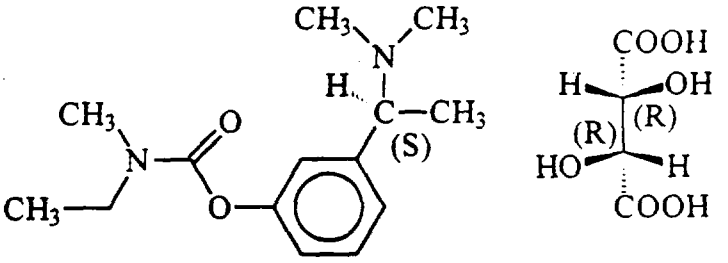
PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type

DOSAGE FORM: Capsules
STRENGTHS: 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8



SUPPORTING DOCUMENTS:
(see Review Notes)
RELATED DOCUMENTS:
REMARKS/COMMENTS: Response to deficiency letter. The samples of copies of container labeling are promised to be send separately and are still to be delivered. The issue of degradant and their levels seems to be resolved (see E-mail from Barry Rosloff).
An acceptable Methods Validation Report has been received. The issue of USAN name has been resolved (see the attached).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-823 APPROVABLE subject to review of package labels.

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

cc
Orig. NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by: MEG 2.16.99

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20823/000
Stamp: 07-APR-1997
Regulatory Due: 12-MAY-1999
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1S
Org Code: 120

Action Goal:
District Goal: 06-DEC-1997
Brand Name: EXELON(RIVASTIGMINE TARTRATE)CAPSULES
Estab. Name:
Generic Name: RIVASTIGMINE TARTRATE 0.5MG/1.0MG/1.5MG

Dosage Form: (CAPSULE)
Strength: [redacted], 1.5, 3, 4.5, 6

Application Comment:
FDA Contacts: R. NIGHSWANDER (HFD-120) 301-594-2850 , Project Manager
W. RZESZOTARSKI (HFD-120) 301-594-2850 , Review Chemist
ID = 100858 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-MAY-1998 by M. EGAS (HFD-322) 301-594-[redacted]

Establishment: 2210396
NOVARTIS PHARMA INC (SANDOZ)
59 RT 10
EAST HANOVER, NJ 079361080
DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER
Profile: CHG OAI Status: NONE
Estab. Comment: LAST INSPECTION: 8/31/94 (on 11-APR-1997 by PARKS)
RCD ORIG. NJ SITE TO DO RELEASE AND STABILITY TESTING AND PACKAGING, LABEL DTD 4/20/97.FWD MOST TO ITOB EX TM AND SOME STAB INFO. (on 21-APR-1997 by R. BROWN (HFR-MA350) 908-940-8967)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
OC RECOMMENDATION	11-APR-1997			ACCEPTABLE BASED ON PROFILE	PARKS

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
LICHTSTRASSE 35
BASEL, , SZ ch-4002
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CHG OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
SUBMITTED TO DO	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	14-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-DEC-1997	GMP			IRIVERA
INSPECTION SCHEDULED	03-MAR-1998		27-FEB-1998		EGASM
INSPECTION PERFORMED	21-MAY-1998		23-FEB-1998		EGASM
DO RECOMMENDATION	21-MAY-1998			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	21-MAY-1998			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CSN OAI Status: NONE

Estab. Comment: PLEASE NOTE THAT NOVARTIS IS THE RIGHT NAME FOR SANDOZ+CIBA-GEIGY ! (on 10-APR-1997 by BLUMS)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
OC RECOMMENDATION	11-APR-1997			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9614433
NOVARTIS PHARMANALYTICA SA
VIA SERAFINO BALESTRA 31
LOCARNO, , SZ

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

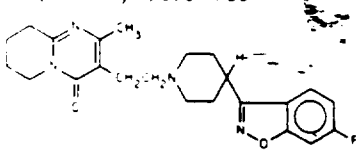
Estab. Comment: NEW ESTABLISHMENT, NOT IN SYSTEM PREVIOUSLY (on 10-APR-1997 by BLUMS)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-APR-1997				BLUMS
SUBMITTED TO DO	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-APR-1997	GMP			EGASM
ASSIGNED INSPECTION	11-DEC-1997	GMP			IRIVERA
INSPECTION SCHEDULED	03-MAR-1998		06-MAR-1998		EGASM
INSPECTION PERFORMED	02-APR-1998		05-MAR-1998		EGASM
OC RECOMMENDATION	02-APR-1998			ACCEPTABLE INSPECTION	EGASM
DO RECOMMENDATION	02-APR-1998			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

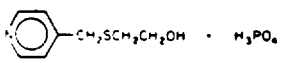
APPEARS THIS WAY ON ORIGINAL

Risperdal. Janssen brand of Risperidone.

Ri **ne** [*1989*] (ris per' i done). $C_{23}H_{27}FN_4O_2$. 410.49. (1) do[1,2-*a*]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benz- -yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2- methyl-; (2) 3-[2-[4-(6-Fluoro-1,2-[redacted]oxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one. *CAS-106266-06-2*. INN; BAN. *Neuroleptic* Risperdal (Janssen) ✧*R 64 766*



Ristianol Phosphate [*1984*] (ris tye' a nole). $C_8H_{11}NOS.H_3PO_4$. 267.24 [Ristianol is INN and BAN.] (1) Ethanol, 2-[(4-pyridinylmethyl)thio]-, phosphate (1:1) (salt); (2) 2-[(4-Pyridylmethyl)thio]ethanol phosphate (1:1) (salt). *CAS-78092-66-7*. *Immunoregulator*. (Pfizer) ✧*CP-48,867-9*

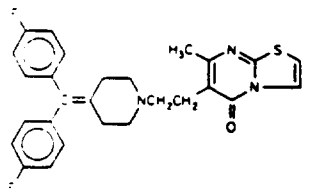


Ristocetin. Antibiotic obtained from cultures of *Nocardia lurida*, or the same substance produced by any other means. *CAS-1404-55-3*. USP XVII; INN; BAN; MI. Spontin (Abbott+)

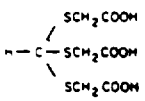
RIT 1149. Code designation for Apicycline.

Ritalin Hydrochloride. Ciba-Geigy brand of Methylphenidate Hydrochloride.

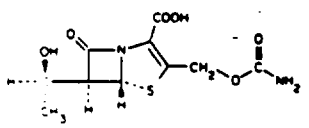
P **rin** [*1985*] (ri tan' ser in). $C_{27}H_{25}F_2N_3OS$. 477.58. (1) hiazolo[3,2-*a*]pyrimidin-5-one, 6-[2-[4-bis(4-fluoro- ylmethylene]-1-piperidinyl]ethyl]-7-methyl-; (2) 6-[2-[4-[Bis(4-fluorophenyl)methylene]-piperidino]ethyl]-7-methyl-5*H*-thiazolo-[3,2-*a*]pyrimidin-5-one. *CAS-87051-43-2*. INN; BAN. *Serotonin antagonist*. Tiserton (Janssen) ✧*R 55,667*



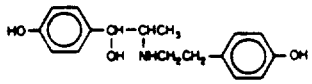
Ritiometan. $C_5H_6O_6S_3$. 286.35. (Methylidynetrithio)triacetic acid. *CAS-34914-39-1*. INN.



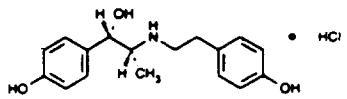
Ritipenem. $C_{10}H_{12}N_2O_6S$. 288.28. **(5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-(hydroxymethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-carbamate.** *CAS-84845-57-5*. INN.



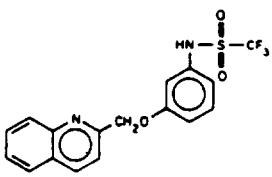
Ritodrine [*1969*] (ri' toe dreen). $C_{17}H_{21}NO_3$. 287.36. (1) Benzenemethanol, 4-hydroxy-α-[1-[[2-(4-hydroxyphenyl)ethyl]-amino]ethyl]-, (*R**,*S**)-; (2) *erythro*-*p*-Hydroxy-α-[1-[(*p*-hydroxyphenethyl)amino]ethyl]benzyl alcohol. *CAS-26652-09-5*. INN; BAN. *Relaxant* (*smooth muscle*). ✧*DU-21220*



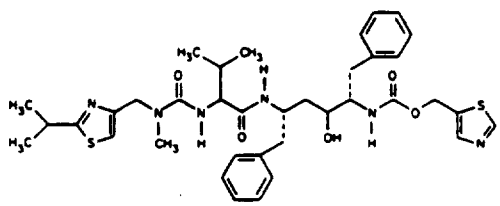
Ritodrine Hydrochloride [*1981*]. USP. $C_{17}H_{21}NO_3.HCl$. 323.82. (1) Benzenemethanol, 4-hydroxy-α-[1-[[2-(4-hydroxyphenyl)ethyl]amino]ethyl]-, hydrochloride, (*R**,*S**)-; (2) *erythro*-*p*-Hydroxy-α-[1-[(*p*-hydroxyphenethyl)amino]-ethyl]benzyl alcohol hydrochloride. *CAS-23239-51-2*. JAN. *Relaxant* (*smooth muscle*). Pre-Par (Philips-Duphar B.V., Netherlands); Yutopar (Astra)



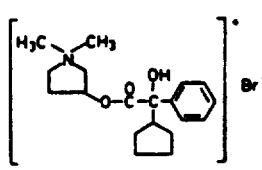
Ritolukast [*1990*] (ri toe' loo kast). $C_{17}H_{13}F_3N_2O_3S$. 382.37. (1) Methanesulfonamide, 1,1,1-trifluoro-*N*-[3-(2-quinolinylmethoxy)phenyl]-; (2) 1,1,1-Trifluoro-α-2-quinolylmethanesulfon-*m*-anisidide. *CAS-111974-60-8*. INN. *Anti-asthmatic* (*leukotriene antagonist*). (Wyeth-Ayerst) ✧*WY-48252*



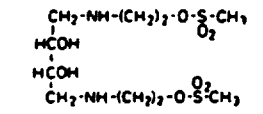
Ritonavir [*1995*] (ri toe' na veer). $C_{37}H_{48}N_6O_5S_2$. 720.96. (1) 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolylmethyl ester [5*S*-(5*R**,8*R**,10*R**,11*R**)]-; (2) 5-Thiazolylmethyl [(α*S*)-α-[(1*S*,3*S*)-1-hydroxy-3-[(2*S*)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]carbamate. *CAS-155213-67-5*. INN. *Antiviral*. Norvir (Abbott) ✧*Abbott-84538*



Ritropirronium Bromide. $C_{19}H_{28}BrNO_3$. 398.34. ***erythro*-3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate.** *CAS-53808-86-9*. INN.



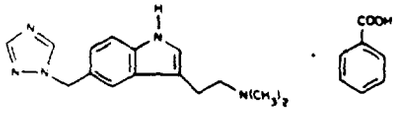
Ritrosulfan. $C_{10}H_{24}N_2O_8S_2$. 364.44. **1,4-Dideoxy-1,4-bis[(2-hydroxyethyl)amino]erythritol 1,4-dimethanesulfonate (ester).** *CAS-4148-16-7*. INN.



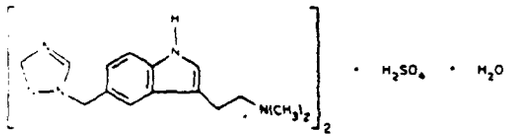
Rituximab [*1997*] (ri tuk' si mab). (1) Immunoglobulin G 1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer; (2) Immunoglobulin G 1 human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer. Molecular weight is approximately 144,187 daltons. *CAS-174722-31-7. Antineoplastic (microtubule inhibitor); monoclonal antibody.* (Idec) ✧*IDEC-C2B8; IDEC-102*

Rivanol. Hoechst-Roussel† brand of Ethacridine Lactate.

Rizatriptan Benzoate [*1996*]. (rye za trip' tan). $C_{15}H_{19}N_5.C_7H_6O_2$. 391.48. [Rizatriptan is INN.] (1) 1*H*-Indole-3-ethanamine, *N*,*N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-, monobenzoate; (2) 3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)indole monobenzoate. *CAS-145202-66-0; CAS-144034-80-0* [rizatriptan]. *Antimigraine.* (Merck) ✧*MK-0462*



Rizatriptan Sulfate [*1996*]. $(C_{15}H_{19}N_5)_2.H_2SO_4.H_2O$. 654.80. (1) 1*H*-Indole-3-ethanamine, *N*,*N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-, sulfate (2:1), monohydrate; (2) 3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)-indole sulfate (2:1), monohydrate. *CAS-159776-67-7; CAS-144034-80-0* [rizatriptan]. *Antimigraine.* (Merck) ✧*MK-0462*



Rizolipase. Lipase of *Rhizopus arrhizus* var. *Delemar*. *CAS-9001-62-1*. INN; DCF.

RM 1601. Code designation for Fipronil.

r-metHuG-CSF. Code designation for Filgrastim.

RMI 8090DJ. Code designation for Quindecamine Acetate.

RMI 9,384A. Code designation for Desipramine Hydrochloride.

RMI 9918. Code designation for Terfenadine.

RMI 10,482A. Code designation for Metizoline Hydrochloride.

RMI 16,238. Code designation for Eterobarb.

RMI 16,289. Code designation for Enclomiphene.

RMI 16,312. Code designation for Zuclomiphene.

RMI 80,029. Code designation for Elantrine.

RMI 81,182EF. Code designation for Cilobamine Mesylate.

RMI 81,968. Code designation for Medroxalol.

RMI 81,968 A. Code designation for Medroxalol Hydrochloride.

RMI 83,027. Code designation for Rolicyprine.

RMI 83,047. Code designation for Ambuside.

RO 1-5155. Code designation for Nicotinyl Alcohol.

† Brand name formerly used, and/or firm no longer concerned with this product.

Ro 01-6794/706; Ro 1-6794 (dextrorphan). Code designation for Dextrorphan Hydrochloride.

Ro 1-9334/19. Code designation for Dehydroemetine.

Ro 1-9569. Code designation for Tetrabenazine.

Ro 2-2985. Code designation for Lasalocid.

Ro 2-3773. Code designation for Clidinium Bromide.

Ro 2-9757. Code designation for Fluorouracil.

Ro 2-9915. Code designation for Flucytosine.

Ro 03-7355/000. Code designation for Avizafone.

Ro 03-8799. Code designation for Pimonidazole.

Ro 4-0403. Code designation for Chlorprothixene.

Ro 4-1544-6. Code designation for Sodium Stibocaptate.

Ro 4-1778/1. Code designation for Methopholine.

Ro 4-2130. Code designation for Sulfamethoxazole.

Ro 4-3780. Code designation for Isotretinoin.

RO 4-3816. Code designation for Alcuronium Chloride.

Ro 4-4393. Code designation for Sulfadoxine.

Ro 4-4602. Code designation for Benserazide.

Ro 4-5282. Code designation for Mefenorex Hydrochloride.

Ro 4-5360. Code designation for Nitrazepam.

Ro 4-6467/1. Code designation for Procarbazine Hydrochloride.

Ro 5-0690. Code designation for Chlordiazepoxide Hydrochloride.

Ro 5-2092. Code designation for Demoxepam.

Ro 5-2807. Code designation for Diazepam.

Ro 5-3059. Code designation for Nitrazepam.

RO 5-3307/1. Code designation for Debrisoquin Sulfate.

Ro 5-3350. Code designation for Bromazepam.

Ro 5-4023. Code designation for Clonazepam.

Ro 5-4200. Code designation for Flunitrazepam.

Ro 5-4556. Code designation for Medazepam Hydrochloride.

Ro 5-4645/010. Code designation for Coumermycin Sodium.

Ro 5-6901. Code designation for Flurazepam Hydrochloride.

Ro 5-9110/1. Code designation for Dorastine Hydrochloride.

Ro 5-9754. Code designation for Ormetoprim.

Ro 6-4563. Code designation for Glibornuride.

Ro 7-0207. Code designation for Ornidazole.

Ro 7-0582. Code designation for Misonidazole.

Ro 7-1554. Code designation for Ipronidazole.

Ro 7-4488/1. Code designation for Cuprimyxin.

Ro 09-1978/000. Code designation for Capecitabine.

Ro 10-1670/000. Code designation for Acitretin.

Ro 10-6338. Code designation for Bumetanide.

Ro 10-9070. Code designation for Amdinocillin.

Ro 10-9071. Code designation for Amdinocillin Pivoxil.

Ro 10-9359. Code designation for Etretinate.

Associate Director
DRA-CMC

Tel 973 781-7005
Fax 973 781-6325
Internet: Robert.Clark
@pharma.novartis.com

NOVARTIS

Fax

Attention: Dr. Waclaw Rzeszotarski
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Fax no.: (301) 594-2859
Number of pages: 5 including cover page

Date: February 11, 1999

Concerning: **USAN/Rivastigmine**

Dear Dr. Rzeszotarski:

Please find enclosed copies of correspondence pertaining to the USAN adoption of the name Rivastigmine for Exelon® Capsules. Please note that in our letter to FDA dated August 25. 1997 (enclosed) Novartis will be designating the generic name for the active ingredient as rivastigmine tartrate. Please note that this designation will be used to describe the active ingredient for all Exelon® products and that the USAN designation does not specify a particular dosage form.

If you have any questions or comments please do not hesitate to contact Sheryl LeRoy at (973) 781-2735 for all CMC issues and Robert Kowalski at (973) 781-6869 for all other issues.

Sincerely,

Robert J. Clark DRA-CMC

Robert W. Kowalski, PharmD
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel (973) 503-6869
Fax (973) 503-6325
Internet: robert.kowalski
@pharma.novartis.com

NOVARTIS

August 25, 1997

Paul Leber, MD
Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Control Room 10B-04
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-823

EXELON™ (rivastigmine tartrate)
Capsules

AMENDMENT TO NDA

Dear Dr. Leber,

Please refer to our New Drug Application for Exelon™ Capsules submitted on April 7, 1997 wherein the established (i.e., non-proprietary or "generic") name for Exelon was noted as

Since the above noted NDA submission, Novartis has received correspondence from the United States Adopted Names (USAN) Council indicating that they have adopted the name of "rivastigmine" for Exelon. Thus, we hereby amend our pending NDA accordingly such that all references in the current application to the established name be changed from
e" to "rivastigmine tartrate".

This change will also be reflected in the revised draft labeling which will be submitted with the impending 120-day safety update.

If you have any comments or questions with regard to this submission, please contact the undersigned at (973) 503-6869.

Sincerely,

Robert W. Kowalski, Pharm.D.
Associate Director,
Drug Regulatory Affairs

Submitted in Duplicate

Desk Copy: R. Nighswander, RPh (HFD-120)

NOVARTIS

PATENT and TRADEMARK DEPARTMENT

FAX (908) 277-4008
PH (908) 277-4256

NOVARTIS CORPORATION
556 Morris Avenue
Summit, NJ 07901-1398

July 25, 1997

Ms. Sophia Fuerst
United States Adopted
Names Council
American Medical Assn.
515 North State Street
Chicago, IL 60610

Re: II-99

Dear Ms. Fuerst:

We acknowledge receipt of your letter dated June 25, 1997 advising of the USAN Council adoption of rivastigmine.

We are herewith providing an amended Statement of Adoption for publication.

Thank you for your kind assistance.

Very truly yours,

Barry A. Solomon
Trademark & Copyright
Counsel

BAS:cp
Enc.

cc: S. Bodmer
R. Kowalski
B. Rosengren

USAN

UNITED STATES ADOPTED NAMES COUNCIL

SOPHIA V. FUERST, Associate Secretary
(312) 464-5352

American Medical Association
515 North State Street
Chicago, Illinois 60610

Telefax: 312-464-4184
E-mail: Sophia_Fuerst@ama-assn.org

June 25, 1997

II-99

Novartis Corporation
556 Morris Avenue
Summit, NJ 07901-1398

Attn: Barry A. Solomon
Trademark & Copyright
Counsel

Dear Mr. Solomon:

It is my pleasure to inform you that the USAN Council adopted **rivastigmine** as the United States Adopted Name for Exelon™; SDZ-ENA-713; SDZ-212-713; ENA-713, Novartis Corporation's acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease.

Enclosed is a copy of the Statement of Adoption on rivastigmine. I plan to schedule publication of this information in the journal of Clinical Pharmacology and Therapeutics unless you request a delay within the next thirty days. Please use the enclosed statement to provide comments or additions. If this information is accurate, and may be published, please initial the statement and return it to me.

Sincerely yours,

Sophia V. Fuerst

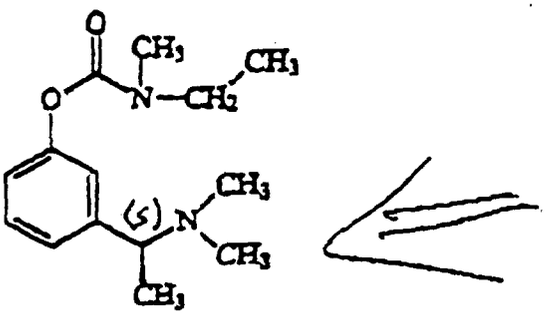
Sophia V. Fuerst
Associate Secretary
USAN Council

SF

Enclosure: N97;59

June 25, 1997

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (II-99)	RIVASTIGMINE
PRONUNCIATION	ri va stig' meen
THERAPEUTIC CLAIMS	Treatment of mild to moderate dementia of the Alzheimer's type (acetylcholinesterase inhibitor)
CHEMICAL NAME	
(1)	
(2)	
STRUCTURAL FORMULA	
MOLECULAR FORMULA	$C_{14}H_{22}N_2O_2$
MOLECULAR WEIGHT	250.34
TRADEMARK	Exelon
MANUFACTURER	Novartis Pharmaceuticals Corporation
CODE DESIGNATIONS	SDZ-ENA-713; SDZ-212-713; ENA-713
CAS REGISTRY NUMBER	[129101-54-8]
WHO NUMBER	7562

SF

BA Salomon 7/28/97

FAX

NOVARTIS CORPORATION
564 Morris Avenue
Summit, N.J.

Trademark And Copyright Group
Fax No. (908) 522-6944
Ph.No. (908) 522-6941

TO: **Bob Clark**
DRA (EH)

February 10, 1999

TOTAL PAGES SENT: 5
(including cover page)

FROM: **Barry Solomon**

FAX #(973) 781-6325

Subject: USAN/Rivastigmine

Per your phone message of this afternoon attached you will find the information you requested.

Regards,

Barry Solomon
Vice President & Counsel

BAS:bi

Attachment

COMPLETION OF MV REVIEW

To: The File

From: *W. Janusz Rzeszotarski, Ph.D.*

Date: *04-MAR-1999*

NDA/ANDA No: *20-823*
Product: *EXELON (rivastigmine tartrate) capsules*
Date of Approval: *PN*

The review of the analytical methods has been completed. The methods have been verified by FDA laboratory and found to be satisfactory. These are now the regulatory methods.

Additional comments: See the note from Moheb M. Nasr (DTAAD) from 01-APR-98.

/S/

W. Janusz Rzeszotarski, Ph.D.

file

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Testing and Applied Analytical Development
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2136
FAX Tel (314) 539-2113

Date: April 1, 1998

From: Moheb M. Nasr, Ph.D., Deputy Director, Laboratory I (HFD-920)

Subject: **Methods Validation for EXELON Bulk Drug and Capsules, NDA 20-823**

TO : W. Janusaz Rzeszotarski, Ph.D., Review Chemist
Food and Drug Administration
DNDCI, ONDC, CDER, HFD-120
Telephone: (301) 594-2850

The evaluation of EXELON Bulk Drug and Capsules MVP, NDA 20-823 has been completed. All methods are suitable for quality control and regulatory purposes. Please refer to specific comments from the evaluating chemist, B.J. Westenberger presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. **We shall retain the reserve samples for 90-days before disposal of remaining samples.** If you feel that the reserve sample should be held longer, please contact DTAAD.

/S/

Moheb M. Nasr, Ph.D.
Deputy Director, Laboratory I

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

FEB 28 2000

NDA #: 20-823 CHEM.REVIEW # 4 REVIEW DATE: 23-FEB-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT (AZ)	21-OCT-99	21-OCT-99	21-OCT-99

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

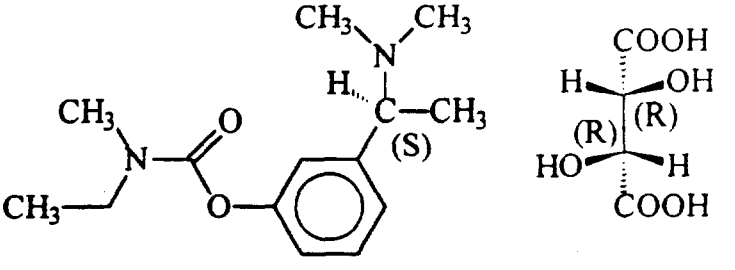
Proprietary: EXELON® Capsules
Nonproprietary/USAN: Rivastigmine Tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase

PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type
DOSAGE FORM:
STRENGTHS: Capsules
ROUTE OF ADMINISTRATION: [redacted], 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
DISPENSED: Oral
XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8



SUPPORTING DOCUMENTS: [redacted]

REMARKS/COMMENTS: Complete Response to the "approvable" letter of 12-MAY-99. Also as discussed between Ms. Sheryl LeRoy of Novartis and Dr. Rzeszotarski of FDA, the present submission includes an Amendment to the Chemistry, Manufacturing & Controls (CMC) section of the NDA. The primary purpose of this amendment is to provide for an alternate site of manufacture and release testing of the drug product. The Novartis Pharma Basel, Switzerland facility is currently listed in original NDA to perform these activities and Novartis plans to phase-out production at this site by the end of the year. Therefore, it was necessary to amend the NDA to provide for the new site at this time. The amendment also provides data to claim an extension of the expiration dating from 2 to 3 years. Also as requested in the May 12 approvable letter, samples of the 6.0 mg capsules have been provided so that the readability of "red" text on a "red/orange" capsule body can be assessed. See a copy of E-mail attached. EER attached.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-823 APPROVABLE with 3 years expiration date subject to review of package labels and acceptable inspection results of an alternative manufacturing site at Stein, Switzerland.

cc:
Orig. NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by: MEG 2/23/00

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

MAR 16 2000

NDA #: 20-823 CHEM.REVIEW # 5 REVIEW DATE: 16-MAR-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT (BF)	10-MAR-00	13-MAR-00	15-MAR-00

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

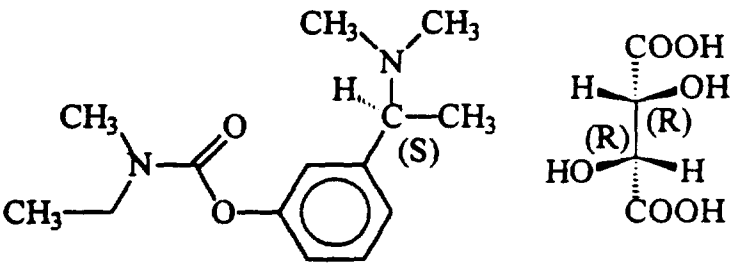
DRUG PRODUCT NAME

Proprietary: EXELON® Capsules
Nonproprietary/USAN: Rivastigmine Tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase
PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type
DOSAGE FORM: Capsules
STRENGTHS: 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8



SUPPORTING DOCUMENTS:

REMARKS/COMMENTS: FINAL PRINTED LABELING. The changes requested have been introduced: 1) the old [redacted] has been replaced by "Rx Only", 2) the term [redacted] has been removed from the sample package cartons, 3) the name "[redacted]" has been modified to "Exelon (rivastigmine tartrate) capsules, 4) [redacted] are thus omitted, and 5) the correct address of manufacturing site entered on the labels.

CONCLUSIONS & RECOMMENDATIONS: The only issues remaining are: 1) the improper font in the professional sample package, making the reading of the generic name difficult (see copy of E-mail attached), and 2) the expected results of inspection of the Stein, Switzerland facility. Recommend the NDA 20-823 approvable until the inspection results are in.

cc:
Orig. NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by: MEG

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

Mangkan
MAR 27 2000

NDA #: 20-823 CHEM.REVIEW # 6 REVIEW DATE: 27-MAR-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
EER	27-MAR-00	27MAR-00	27-MAR-00

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary: EXELON® Capsules
Nonproprietary/USAN: Rivastigmine Tartrate
Code Name/#: ENA 713
Chem.Type/Ther.Class: Pseudo-irreversible inhibitor of acetylcholine esterase
PHARMACOL.CATEGORY/INDICATION: Mild to moderate dementia of the Alzheimer's type
DOSAGE FORM: Capsules
STRENGTHS: ~~~~ mg; 1.5 mg; 3.0 mg; 4.5 mg & 6.0 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

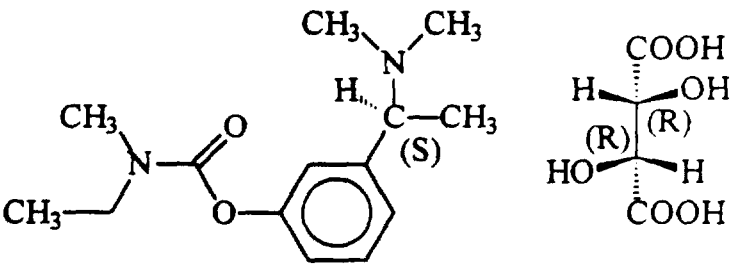
(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate hydrogen-(2R,3R)-tartrate

$C_{14}H_{22}N_2O_2$. $C_4H_6O_6$ = $C_{18}H_{28}N_2O_8$; Molecular Weight: 250.3 + 150.1 = 400.4;
CAS #: 129101-54-8

SUPPORTING DOCUMENTS: IND 35,774, DMFs (see Review Notes)

REMARKS/COMMENTS: ESTABLISHMENT EVALUATION REPORT: Provided overall recommendation as acceptable.

CONCLUSIONS & RECOMMENDATIONS: The sponsor should commit to change the font in the professional sample package since the present is making the reading of the generic name difficult (see copy of E-mail attached). There are no other CMC issues to correct. Recommend the approval of the NDA 20-823. Copy of the final EER attached



/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

cc:
Orig. NDA 20-823
HFD-120
HFD-120/WJRzeszotarski
HFD-120/RNighswander
HFD-120/MEGuzewska
HFD-810/JSimmons
R/D Init by: MEG

filename: E:\msword\n20823r.006